ClinicalEvidence

Opioids in people with cancer-related pain

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ABSTRACT

INTRODUCTION: Up to 80% of people with cancer experience pain at some time during their illness, and most will need opioid analgesics. This review assesses how different opioid analgesics compare, in terms of both pain control and adverse effects, in people with cancer. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: what are the effects of opioids in treating cancer-related pain? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2007 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 22 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: codeine, dihydrocodeine, transdermal fentanyl, hydromorphone, methadone, morphine, oxycodone, and tramadol.

QUESTIONS

INTERVENTIONS

Key points

- Up to 80% of people with cancer experience pain at some time during their illness, and most will need opioid analgesics. This review focuses on assessing how different opioid analgesics compare, in terms of both pain control and adverse effects, in people with cancer.
- Oral morphine is the standard treatment for the management of moderate to severe cancer-related pain. Despite lack of large, robust clinical trials, morphine is, to date, the most tried-and-tested opioid for this indication.
- There are an increasing number of opioids now available that are also effective for the same clinical indication. However, we found insufficient evidence to assess the equivalence, in terms of analgesic benefit and adverse effects, of morphine compared with codeine, dihydrocodeine, fentanyl, hydromorphone, methadone, oxycodone, or tramadol.

DEFINITION

Up to 80% of people with cancer experience pain at some time during their illness, and most will need opioid analgesics. [1] This review focuses on assessing how different opioid analgesics compare, in terms of both pain control and adverse effects, in people with cancer. For the purposes of this review, we have used the NICE definition of supportive care as follows: supportive care "helps the patient and their family to cope with cancer and treatment of it — from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment". [2] This definition was written in relation to people with cancer, but is applicable to all people with chronic or terminal illness: for example, heart failure or lung disease. We have used the WHO definition of palliative care as follows: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual". [3] Although this definition of palliative care does not specify incurable or terminal illness, there is consensus that palliative care applies to people approaching the end of life: that is, in the last year or less. Thus, both supportive and palliative care embrace the same priorities of maximising quality of life, although supportive care aims to do this in people who may live longer, become cured, or who are living in remission from their disease.

INCIDENCE/ PREVALENCE	One population-based survey of 3030 people with cancer from 143 palliative care centres in 21 European countries found that most (97%) people received analgesics: 32% were assessed as having moderate or severe pain. [4] Morphine was the most frequently used opioid for moderate to severe pain (oral normal-release morphine: 21%; oral sustained-release morphine: 19%; intravenous or subcutaneous morphine: 10%). Other opioids used for moderate to severe pain were transdermal fentanyl (14%), oxycodone (4%), methadone (2%), diamorphine (2%), and hydromorphone (1%). Opioids administered for mild to moderate pain were codeine (8%), tramadol (8%), dextropropoxyphene (5%), and dihydrocodeine (2%). The survey observed large variations in the use of opioids across countries.
AIMS OF INTERVENTION	To achieve level of pain control acceptable to the individual, with minimal adverse effects of treatment.
OUTCOMES	Pain, need for rescue analgesia, function, quality of life, patient preference, adverse effects.
METHODS	*BMJ Clinical Evidence* search and appraisal July 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2007, Embase 1980 to July 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language and containing more than 20 individuals, of whom more than 50% were followed up. There was no minimum length of follow-up required to include RCTs and we included open label RCTs. We use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15).

QUESTION What are the effects of opioids in treating cancer-related pain?

OPTION MORPHINE New

Pain control

Compared with fentanyl (transdermal) We don't know whether morphine is more effective at controlling cancer-related pain (very low-quality evidence).

Oral morphine compared with oral methadone We don't know whether oral morphine is more effective at reducing cancer-related pain (very low-quality evidence).

Parenteral morphine compared with parenteral methadone We don't know whether parenteral morphine is more effective at reducing cancer-related pain (very low-quality evidence).

Compared with oxycodone We don't know whether morphine is more effective at reducing cancer-related pain at 4–14 days (low-quality evidence).

Compared with tramadol We don't know whether morphine is more effective at reducing cancer-related pain at 2–5 weeks (very low-quality evidence).

Need for rescue analgesia

Compared with fentanyl (transdermal) We don't know whether morphine is more effective at reducing the need for rescue analgesia for breakthrough pain in people with cancer (very low-quality evidence).

Compared with hydromorphone We don't know whether morphine is more effective at reducing the need for rescue analgesia over the last 24 hours of treatment in people with cancer-related pain (very low-quality evidence).

Patient preference

Compared with fentanyl (transdermal) We don't know whether people with cancer prefer morphine to transdermal fentanyl (very low-quality evidence).

Compared with tramadol Morphine may be the preferred opioid when balancing between pain control and adverse effects (very low-quality evidence).

Compared with oxycodone We don't know whether morphine is preferred to oxycodone (low-quality evidence).

Adverse effects
Compared with fentanyl (transdermal) Morphine may be more likely to cause adverse effects (particularly constipation and drowsiness), and may increase the proportion of people who withdraw from treatment (low-quality evidence).

Note
Oral morphine is the standard for the management of moderate to severe cancer-related pain and is, to date, the most tried-and-tested opioid for this indication. We found no clinically important results about morphine compared with codeine or dihydrocodeine in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Morphine versus placebo:
We found no systematic review or RCTs.

Morphine versus fentanyl (transdermal):
We found two systematic reviews (search date 2002, [5] search date 2004 [6]), which identified three RCTs that met *BMJ Clinical Evidence* quality criteria, comparing morphine versus transdermal fentanyl. The first review did not perform a meta-analysis, and the second review meta-analysed both RCTs and uncontrolled trials; therefore we report the individual RCT results here. [7] [8] [9] The first RCT (202 people with terminal-cancer pain, open label crossover design) identified by the reviews compared sustained-release oral morphine (30 or 60 mg according to clinical need) and transdermal fentanyl (2.5, 5.0, 7.5, or 10 mg according to clinical need) for 15 days. [8] It found no significant difference in pain at 30 days after crossover (proportion of people who rated pain control as successful: 99/122 [81%] with morphine *v* 94/122 [77%] with fentanyl; reported as non-significant; P value not reported). [8] The RCT assessed potential carryover effects, and found no significant difference between groups for this outcome. It found that significantly fewer people taking morphine than fentanyl required rescue analgesia over the first week of treatment before crossover (proportion of days where analgesia needed: 43% with morphine *v* 54% with fentanyl; P = 0.0005; absolute numbers not reported). This difference remained significant during the second week of treatment before crossover, although need for rescue analgesia was lower in both groups (28% with morphine *v* 31% with fentanyl; P = 0.03; absolute numbers not reported). Analysis of 136 participants who stated a treatment preference found that significantly more people preferred fentanyl to morphine (proportion who preferred treatment: 49/136 [36%] with morphine *v* 73/136 [54%] with fentanyl; P = 0.04). The second RCT (47 people with cancer requiring strong opioid analgesia, all of whom had received immediate-release morphine for 7 days, open label parallel design) identified by the reviews compared oral sustained-release morphine (dose not reported, administered every 12 hours) versus transdermal fentanyl (patches released between 25 and 300 mcg every hour, doses varied according to need) for 14 days. [7] Analysis of 20 people who completed the trial found no significant difference in pain over 14 days (measured on a scale from 0–4: 0.85 with morphine *v* 0.9 with fentanyl; reported as non-significant; P value not reported). [7] The RCT also found no significant difference between groups in the rescue doses of morphine required for breakthrough pain over 14 days (26 doses with morphine *v* 21 doses with fentanyl; reported as non-significant; P value not reported). The third RCT (131 people with cancer pain, open label parallel design) identified by the reviews compared sustained-release morphine (30 mg every 12 hours for 3 days, then titrated according to need, average maximal dose of 105 mg hourly, range 30–400 mg daily) versus transdermal fentanyl (25 mcg hourly for 3 days, then titrated according to need, average maximal dose of 67 mcg hourly, range 25–400 mcg hourly) for 4 weeks. [9] It found no significant difference in pain at 28 weeks between morphine and transdermal fentanyl (decrease in pain on a scale from 1–10 where 1 = no pain and 10 = pain as bad as you can imagine: 1.1 with morphine *v* 1.5 with fentanyl; P = 0.31). [9] It also found no significant difference between groups in patient preference (overall rating on a scale from 0–10 where 0 = very poor and 10 = very good: 3.3 with morphine *v* 4.3 with fentanyl; P = 0.30).

Morphine versus hydromorphone:
We found two systematic reviews (search date 2002, [5] search date 2000 [10]), which identified two RCTs comparing morphine versus hydromorphone. One of the RCTs was unpublished, and the authors of the reviews were unable to obtain further details of the trial, so it is not reported further here. Neither review performed a meta-analysis. The published RCT (100 people aged at least 18 years with cancer-related pain, double blind crossover design) identified by the reviews compared sustained-release morphine (dose not reported) versus sustained-release hydromorphone (dose not reported) for two 3-day treatment periods. [11] The dose of hydromorphone was based on the assumption that hydromorphone is 7.5 times more potent than morphine. The primary outcome measure was use of rescue analgesia over the last 24 hours of each treatment period. The RCT assessed outcomes after crossover in 89/100 [89%] people who completed the trial. It found no significant difference in use of rescue analgesia over the last 24 hours of treatment between morphine and hydromorphone (0.1 times in each treatment group; P less than 0.08). As there was no washout between treatments, there may have been carryover effects, making it difficult to assess

possible differences between groups. Pain scores were also generally low in both groups, with overall pain visual analogue scale (VAS) less than 11 mm on a 100 mm VAS; 70/89 (79%) people analysed did not require rescue analgesia with either treatment. This, together with the weak methods of the trial, make its results difficult to apply to clinical practice.

Oral morphine versus oral methadone:
We found two systematic reviews (search dates 2002 [5] [12]), which identified two RCTs comparing oral morphine versus oral methadone. [13] [14] We also found one subsequent RCT. [15] The first RCT (40 people with advanced cancer and pain, open label parallel design) identified by the reviews compared sustained-release oral morphine (10, 30, 60, or 100 mg according to clinical need every 8–12 hours) versus oral methadone (0.1% 2 or 3 times daily) given at home two to three times a week until death. [13] It found similar pain reductions during treatment (duration not specified) with morphine and methadone (mean score on a VAS from 0–10 cm: 3.3 with morphine *v* 3.4 with methadone; significance not reported). The second RCT (66 people with advanced cancer and severe pain, open label parallel design) identified by the reviews compared sustained-release oral morphine (72.7–119.4 mg, average daily dose given according to patient need) versus oral methadone (18 mg, average daily dose given according to patient need) for 14 days. [14] Results in 54/66 (82%) people found no significant difference in pain between groups, with both morphine and methadone reducing pain intensity over 14 days (reported as non-significant, absolute results presented graphically; P value not reported). The subsequent RCT (103 people with cancer-related pain, double blind parallel design) compared oral morphine (slow-release 15 mg twice daily, or immediate-release 5 mg every 4 hours, as needed) versus oral methadone (7.5 mg every 12 hours, 5 mg every 4 hours, as needed). [15] The RCT found no significant difference in pain at day 8 between morphine and methadone, although more than three quarters of people in each group had pain reduction (proportion with 20% or more reduction in pain intensity: 24/49 [49%] with morphine *v* 30/54 [56%] with methadone; P = 0.50). It also found no significant difference in patient-reported global benefit between morphine and methadone (proportion who reported benefit: 61% with morphine *v* 50% with methadone; P = 0.41; absolute numbers not reported). The RCT may have been too small to detect a clinically important difference between groups; it did not meet the accrual goal of 100 participants in each treatment arm, and therefore only had sufficient power to detect a difference in response rates of 30% or greater.

Parenteral morphine versus parenteral methadone:
We found two systematic reviews (search dates 2002 [5] [12]), which identified two RCTs comparing intravenous morphine versus intravenous or intramuscular methadone. [16] [17] The first RCT (37 people in hospital with chronic cancer-related pain, double blind parallel design) compared intramuscular morphine versus intramuscular methadone. [16] All participants also received an additional analgesic (not specified). The RCT used a crossover design alternating morphine 8–16 mg or methadone 16–48 mg in series. Treatment was given as needed, but no more often than every 3 hours. Results combining all four series after crossover found similar reductions in pain intensity at 2–6 hours after treatment with both morphine and methadone (proportion of people reporting reduction in pain of at least 50%: 53% with morphine 20.8 mg *v* 55% with methadone 25.8 mg; no further data reported). The second RCT (23 people with cancer-related pain, 18 evaluated, double blind parallel design) found no significant difference between intravenous morphine (2–120 mg given according to patient need) and intravenous methadone (4–57 mg initial dose range, 6–85 mg final dose range given according to patient need) in pain intensity over 4 hours after treatment (P = 0.94, absolute numbers presented graphically). [17]

Morphine versus oxycodone:
We found three systematic reviews (search dates 2002, [5] [18] and 2000 [19]), which identified the same four RCTs. One of the reviews meta-analysed three of the RCTs, and found no significant difference in pain over 12–14 days between oxycodone and morphine (178 people: SMD 0.20, 95% CI –0.04 to +0.44; absolute numbers not reported). [18] Mean dose of morphine in the trials was 140–180 mg every 24 hours. Mean oxycodone dose was 90–150 mg every 24 hours. The fourth RCT (20 people with severe cancer-related pain, double blind crossover design) identified by the reviews could not be included in the meta-analysis owing to weak reporting of data. [20] It compared intravenous followed by oral morphine (iv mean dose 75 mg, range 25–130 mg; oral mean dose 204 mg, range 72–360 mg, dose by patient-controlled titration) versus intravenous followed by oral oxycodone (iv mean dose 84 mg, range 41–147 mg; oral mean dose 150 mg, range 57–301 mg, dose by patient-controlled titration) for 4 days. [20] It found no significant difference in pain over 4 days after crossover between morphine and oxycodone (measured on a 10 cm VAS: reported as non-significant; absolute numbers and P value not reported). [20] The RCT found that patient preference was equivalent, with 5/10 [50%] people preferring morphine and 5/10 [50%] oxycodone (significance not reported).

Morphine versus tramadol:
We found one systematic review (search date 2002), [5] which identified two RCTs. [21] [22] The first RCT (40 people with cancer-related or other neuropathic pain, open label parallel design) identified by the reviews found that morphine 20–200 mg daily caused significantly better relief for neuropathic pain at 1 week compared with tramadol 150–600 mg daily (neuropathic pain on a 100 mm VAS: 19.25 with morphine *v* 57.00 with tramadol; P less than 0.05). [22] However, neuropathic pain relief was similar in both groups at weeks 2, 3, 4, and 5. The RCT did not report how initial doses of morphine and tramadol were assessed in order to ensure equivalent potency between the drugs. The number of people with the sub-category of cancer-related neuropathic pain was not reported, making it difficult to draw conclusions from this study. The authors of the reviews were unable to gain any additional data from the original authors of the RCT. The second RCT [21] (20 people with cancer-related pain that had not responded to previous pain treatment [previous treatment not reported], double blind crossover design) identified by the reviews compared morphine 16 mg versus tramadol 50 mg every 4 hours for 8 days (crossover at 4 days). [21] The RCT found that morphine significantly reduced daily pain score on days 1–2 compared with tramadol, but found similar pain scores between groups on day 4 (20 people evaluated, pain assessed using a 5-point verbal rating scale where 0 = none and 4 = unbearable; P less than 0.01 at day 1–2, absolute results presented graphically; mean score 1.6 with morphine *v* 1.5 with tramadol at day 4; P value not reported). The RCT found that more people preferred morphine to tramadol when balancing pain control and adverse effects in their assessment, but it did not assess the significance of the difference between groups (9/20 [45%] preferred morphine *v* 3/20 [15%] with tramadol; P value not reported).

Morphine versus codeine or dihydrocodeine:
We found no systematic review or RCTs.

Harms:

Morphine versus placebo:
We found no RCTs.

Morphine versus fentanyl (transdermal):
The first RCT identified by the reviews found that morphine and fentanyl were associated with drowsiness in a similar proportion of people in both groups (6/122 [5%] with morphine *v* 5/122 [4%] with fentanyl; significance not assessed). [8] The second RCT identified by the reviews found that morphine was associated with significantly more constipation (mean score on a scale from 0–100: 36.6 with morphine *v* 20.7 with fentanyl; P less than 0.001) and more daytime drowsiness (43.5 with morphine *v* 34.0 with fentanyl; P = 0.02) compared with fentanyl, but less sleep disturbance (22.4 with morphine *v* 32.4 with fentanyl; P = 0.004). [7] The third RCT identified by the reviews found that significantly more people taking morphine than transdermal fentanyl withdrew because of adverse effects (23/64 [36%] with morphine *v* 3/67 [4%] with fentanyl; P less than 0.001). [9] The most common adverse effects were nausea and vomiting, drowsiness, and constipation. The second review, which meta-analysed both RCTs and uncontrolled trials, found that, when analysing people with cancer pain, morphine was associated with significantly more adverse effects deemed to be drug related compared with transdermal fentanyl (342 people: 71% with morphine *v* 40% with fentanyl; P less than 0.001). It also found that morphine significantly increased the proportion of people who withdrew because of adverse effects (93 people, 34% with morphine *v* 7% with fentanyl; P less than 0.001). People receiving morphine had significantly more somnolence compared with people receiving fentanyl (25% with morphine *v* 13% with fentanyl; P less than 0.001). There was no significant difference in nausea and vomiting between morphine and fentanyl (32% with morphine *v* 34% with fentanyl; P = 0.63; absolute results not reported for any outcome). [6]

Morphine versus hydromorphone:
The first RCT identified by the reviews found no significant difference in nausea or sedation over the last 24 hours of each treatment period between morphine and hydromorphone (reported as non-significant, absolute numbers and P values not reported). [11]

Oral morphine versus oral methadone:
The first RCT identified by the reviews did not assess the significance of the difference between groups when assessing adverse effects. [13] It found that both morphine and methadone were associated with nausea and vomiting, drowsiness, dry mouth, and constipation (absolute data not interpretable as scale for numbers reported was unclear). The second RCT identified by the reviews found that morphine significantly increased dry mouth compared with methadone (P less than 0.01), whereas methadone significantly increased headache (P less than 0.01, absolute results presented graphically for both outcomes). [14] Both drugs were associated with drowsiness and constipation, with no significant difference between groups (reported as non-significant, absolute results presented graphically for both outcomes). The subsequent RCT found no significant difference between morphine and methadone in the proportion of people with adverse effects including sedation, nausea, confusion, and constipation (proportion with increase in adverse effects of 20%

or more: 36/54 [66.6%] with morphine *v* 33/67 [67.3%] with methadone; P = 0.68). [15] However, withdrawals because of adverse effects were significantly higher in people taking methadone (11/49 [22%] with methadone *v* 3/54 [6%] with morphine; P = 0.02).

Parenteral morphine versus parenteral methadone:
The first RCT identified by the reviews found no significant difference in rates of adverse effects between morphine and methadone (reported as P greater than 0.05, absolute numbers not reported). [16] Adverse effects of both drugs included nausea and vomiting, sedation, and dizziness. The second RCT identified by the reviews did not assess the significance of the difference in adverse effects between groups, but suggested that both drugs were associated with sedation (6/10 [60%] with morphine *v* 5/8 [62%] with methadone). Both drugs were also associated with nausea, dry mouth, constipation, and difficulty concentrating (no further data reported).

Morphine versus oxycodone:
One of the reviews found that morphine significantly increased dry mouth and drowsiness compared with oxycodone (dry mouth: OR 0.56, 95% CI 0.38 to 0.83; drowsiness: OR 0.72, 95% CI 0.47 to 1.10; absolute numbers not reported for either outcome). [18] The fourth RCT identified by the reviews found that sedation was the most common adverse effect of both morphine and oxycodone (absolute numbers not reported for each participant; significance not reported). [20] The RCT did not assess the significance of the difference between groups in any adverse effect, reporting that both drugs were also associated with nausea and constipation.

Morphine versus tramadol:
The first RCT identified by the reviews found that morphine was associated with significantly more drowsiness, difficulty in passing urine, dizziness, and sweating compared with tramadol (reported as significant for all outcomes, no further data reported). [22] The second RCT (20 people) identified by the reviews found that more people taking morphine withdrew because of adverse effects (nausea and vomiting or dizziness: 3/20 [15%] with morphine *v* 0/20 [0%] with tramadol; significance not assessed). [21]

Morphine versus codeine or dihydrocodeine:
We found no RCTs.

Comment:

Clinical guide:
Although available evidence fails to support superiority of alternative opioids to morphine, further research is needed to investigate true opioid differences in terms of analgesic efficacy and adverse-effect profile. Current evidence suggests that, at equianalgesic doses (which is a controversial issue), morphine remains the standard for the management of moderate to severe cancer pain. Alternative opioids may have a specific role in cancer pain management. However, further studies are needed to confirm this.

OPTION CODEINE New

Pain control
Compared with placebo Codeine may be more effective at reducing chronic cancer pain at 2 weeks (low-quality evidence).

Compared with tramadol We don't know whether codeine is more effective at reducing cancer-related pain (very low-quality evidence).

Need for rescue analgesia
Compared with placebo Codeine may be more effective at reducing the need for rescue analgesia in people with chronic cancer pain (low-quality evidence).

Patient preference
Compared with tramadol We don't know whether people prefer codeine to tramadol (very low-quality evidence).

Note
We found no clinically important results about codeine compared with morphine, dihydrocodeine, transdermal fentanyl, hydromorphone, methadone, or oxycodone in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Codeine versus placebo:
We found one RCT (35 people with chronic cancer pain, double blind crossover design) comparing codeine mean 277 mg daily (controlled-release) versus placebo every 12 hours for 2 weeks. [23] The RCT did not report results before crossover, but reported no significant carryover effects. At

2 weeks, results in 30/35 (86%) participants found that codeine significantly reduced pain compared with placebo (overall pain intensity scores measured on a 100 mm visual analogue scale: 22 mm with codeine *v* 36 mm with placebo; P = 0.0001). It also found that codeine significantly reduced the need for rescue analgesia compared with placebo (mean consumption of rescue analgesia: 2.2 tablets daily with codeine *v* 4.6 with placebo; P = 0.0001). Patient satisfaction was also significantly higher with codeine compared with placebo (80% stated that they preferred codeine *v* 3% stated that they preferred placebo; P = 0.001, absolute numbers not reported). [23]

Codeine versus morphine, dihydrocodeine, transdermal fentanyl, hydromorphone, methadone, or oxycodone:
We found no systematic review or RCTs.

Codeine versus tramadol:
See benefits of tramadol**.**

Harms:

Codeine versus placebo:
The RCT found no significant difference between codeine and placebo in adverse effects, other than for nausea, which was significantly higher in people taking codeine (40% with codeine *v* 15% with placebo; P = 0.01, absolute numbers not reported).

Codeine versus morphine, transdermal fentanyl, hydromorphone, methadone, oxycodone, or tramadol:
We found no RCTs.

Comment: None.

OPTION DIHYDROCODEINE New

Pain control
Compared with tramadol We don't know whether dihydrocodeine is more effective at relieving prostate cancer-related pain (very low-quality evidence).

Patient preference
Compared with tramadol We don't know whether people prefer dihydrocodeine to tramadol for prostate cancer-related pain (very low-quality evidence).

Note
We found no clinically important results about dihydrocodeine compared with no active treatment or morphine, codeine, transdermal fentanyl, hydromorphone, methadone, or oxycodone in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Dihydrocodeine versus placebo:
We found no systematic review or RCTs.

Dihydrocodeine versus tramadol:
See benefits of tramadol.

Dihydrocodeine versus morphine, codeine, transdermal fentanyl, hydromorphone, methadone, or oxycodone:
We found no systematic review or RCTs.

Harms:

Dihydrocodeine versus placebo:
We found no RCTs.

Dihydrocodeine versus tramadol:
See harms of tramadol.

Dihydrocodeine versus morphine, codeine, transdermal fentanyl, hydromorphone, methadone, or oxycodone:
We found no RCTs.

Comment: None.

OPTION FENTANYL (TRANSDERMAL) New

Pain control

Compared with placebo Transdermal fentanyl may be no more effective at reducing pain intensity in people with chronic cancer (very low-quality evidence).

Compared with morphine We don't know whether fentanyl (transdermal) is more effective at relieving cancer-related pain (very low-quality evidence).

Need for rescue analgesia
Compared with morphine We don't know whether fentanyl (transdermal) is more effective at reducing the need for rescue analgesia for breakthrough pain in people with cancer (very low-quality evidence).

Patient preference
Compared with morphine We don't know whether people with cancer prefer fentanyl (transdermal) to morphine (very low-quality evidence).

Adverse effects
Compared with morphine Fentanyl (transdermal) may cause fewer adverse effects (particularly constipation, and drowsiness), and may decrease the proportion of people who withdraw from treatment because of adverse effects (low-quality evidence).

Note
We found no clinically important results about transdermal fentanyl compared with codeine, dihydrocodeine, hydromorphone, methadone, oxycodone, or tramadol in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Transdermal fentanyl versus placebo:
We found no systematic review but found one RCT (138 people with chronic cancer pain, double blind design) comparing transdermal fentanyl (mean 65 mcg/hour, dose titrated to achieve adequate pain control) versus placebo (mean 51 mcg/hour) for 9 days. [24] The RCT was preceded by a dose-assessment phase, during which fentanyl dose was titrated to achieve adequate pain control (pain scores no worse than moderate). Results were evaluated in 72/138 (52%) participants. A high placebo response was observed, with no significant difference between groups in terms of pain intensity (pain intensity on waking measured on a 100 mm visual analogue scale: median 1.0 with fentanyl *v* 1.1 with placebo; P greater than 0.05). There was also no significant difference between transdermal fentanyl and placebo in the need for immediate-release morphine as rescue medication (mean 47.7 mg with fentanyl *v* 51.0 mg with placebo; P = 0.21). [24]

Transdermal fentanyl versus morphine:
See benefits of morphine, p 2 .

Transdermal fentanyl versus codeine, dihydrocodeine, hydromorphone, methadone, oxycodone, tramadol:
We found no systematic review or RCTs.

Harms:

Transdermal fentanyl versus placebo:
The RCT did not directly compare adverse effects of fentanyl versus placebo; it found that fentanyl was associated with nausea in 4% of people during the double blind phase of the trial. [24]

Transdermal fentanyl versus morphine:
See harms of morphine, p 2 .

Transdermal fentanyl versus codeine, dihydrocodeine, hydromorphone, methadone, oxycodone, tramadol:
We found no RCTs.

Comment:

Clinical guide:
Transdermal fentanyl is a drug-delivery system that provides continuous administration of fentanyl for 72 hours after each application. While a potentially useful alternative to morphine for the management of cancer-related pain, because of its long duration of action, transdermal fentanyl is generally reserved for patients with stable opioid requirements. It is a strong opioid analgesic, providing similar pain relief to morphine. However, the RCTs we found recruited participants with relatively well-controlled pain, making it difficult to detect 'real' differences between groups. The only placebo-controlled study demonstrated a high placebo analgesic response.

OPTION HYDROMORPHONE New

Pain control

Compared with oxycodone We don't know whether hydromorphone is more effective at reducing pain intensity as measured on a 5-point scale in people with cancer pain (low-quality evidence).

Need for rescue analgesia
Compared with morphine We don't know whether hydromorphone is more effective at reducing the need for rescue analgesia over the last 24 hours of treatment in people with cancer-related pain (very low-quality evidence).

Patient preference
Compared with oxycodone We don't know whether people prefer hydromorphone to oxycodone (low-quality evidence).

Note
We found no clinically important results about hydromorphone compared with codeine, dihydrocodeine, transdermal fentanyl, methadone, or tramadol in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Hydromorphone versus placebo:
We found one systematic review (search date 2000), which identified no RCTs. [10]

Hydromorphone versus morphine:
See benefits of morphine, p 2 .

Hydromorphone versus oxycodone:
See benefits of oxycodone, p 10 .

Hydromorphone versus codeine, dihydrocodeine, transdermal fentanyl, methadone, or tramadol:
We found no systematic review or RCTs.

Harms:

Hydromorphone versus placebo:
We found no RCTs.

Hydromorphone versus morphine:
See harms of morphine, p 2 .

Hydromorphone versus oxycodone:
See harms of oxycodone, p 10 .

Hydromorphone versus codeine, dihydrocodeine, transdermal fentanyl, methadone, or tramadol:
We found no RCTs.

Comment:

Clinical guide:
Hydromorphone is a potent opioid analgesic. At present there is no consistent evidence to suggest that hydromorphone is superior to morphine in terms of analgesic benefit and adverse-effect profile. At equianalgesic doses, both opioids appear to have a similar clinical profile. We found no consistent evidence to suggest that hydromorphone causes more or less toxicity at equivalent analgesic doses to morphine.

OPTION METHADONE New

Pain control
Oral methadone compared with oral morphine We don't know whether oral methadone is more effective at reducing pain in people with cancer (very low-quality evidence).

Parenteral methadone compared with parenteral morphine We don't know whether parenteral methadone is more effective at reducing cancer-related pain (very low-quality evidence).

Note
We found no clinically important results about methadone compared with no active treatment, or with codeine, dihydrocodeine, transdermal fentanyl, hydromorphone, oxycodone, or tramadol in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Methadone versus placebo:
We found no systematic review RCTs.

Methadone versus morphine:
See benefits of morphine, p 2 .

Methadone versus codeine, dihydrocodeine, transdermal fentanyl, hydromorphone, oxycodone, or tramadol:
We found no systematic review or RCTs.

Harms:

Methadone versus placebo:
We found no RCTs.

Methadone versus morphine:
See harms of morphine, p 2 .

Methadone versus codeine, dihydrocodeine, transdermal fentanyl, hydromorphone, oxycodone, or tramadol:
We found no RCTs.

Comment:

Clinical guide:
Available evidence suggests that methadone is an effective analgesic for cancer pain. However, studies to date do not demonstrate an advantage over the current standard treatment for cancer-related pain, morphine. In addition, there is considerable variation in the literature about conversion ratios for methadone and for dose-titration schedules. The long half-life of methadone carries the risk of drug accumulation and latent toxicity. People taking methadone therefore need to be carefully monitored.

OPTION OXYCODONE New

Pain control
Compared with morphine We don't know whether oxycodone is more effective at reducing cancer-related pain at 4–14 days (low-quality evidence).

Compared with hydromorphone We don't know whether oxycodone is more effective at reducing pain intensity as measured on a 5-point scale in people with cancer pain (low-quality evidence).

Patient preference
Compared with morphine We don't know whether people prefer oxycodone to morphine (low-quality evidence).

Compared with hydromorphone We don't know whether people prefer oxycodone to hydromorphone (low-quality evidence).

Note
We found no clinically important results about oxycodone compared with no active treatment, or with transdermal fentanyl, methadone, or tramadol in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Oxycodone versus placebo:
We found no systematic review or RCTs.

Oxycodone versus morphine:
See benefits of morphine, p 2 .

Oxycodone versus hydromorphone:
We found two systematic reviews (search date 2000, [19] search date 2002 [18]), which both identified the same RCT. [25] Neither review reported full data of the RCT, so we report the data from the original paper here. [25] The RCT (44 people with cancer pain, crossover design) compared controlled-release oxycodone (mean 124 mg daily, dose adjusted according to pain level) versus controlled-release hydromorphone (mean 30 mg daily, dose adjusted according to pain level) for 7 days. [25] The RCT found no significant difference between treatments in pain or pain intensity (pain: measured on a 100 mm visual analogue scale [VAS]: 28 with oxycodone *v* 31 with hydromorphone; P = 0.11; pain intensity [measured on a 5-point scale where 0 = none, 1 = mild, and 4 = excruciating]: 1.4 with oxycodone *v* 1.5 with hydromorphone; P = 0.11). There were also similar rates of patient preference between groups (35% with oxycodone *v* 39% with hydromorphone; absolute numbers and P value not reported).

Oxycodone versus transdermal fentanyl, methadone, or tramadol:
We found no systematic review or RCTs.

Harms:

Oxycodone versus placebo:
We found no RCTs.

Oxycodone versus morphine:
See harms of morphine, p 2 .

Oxycodone versus hydromorphone:
The RCT found no significant difference in sedation or nausea scores between hydromorphone and oxycodone (sedation: visual analogue scale 23.6 mm with oxycodone *v* 18.2 mm with hydromorphone; P = 0.11; nausea: visual analogue scale 15.5 mm with oxycodone *v* 13.1 mm with hydromorphone; P = 0.38). [25]

Oxycodone versus transdermal fentanyl, methadone, or tramadol:
We found no RCTs.

Comment:

Clinical guide:
Oxycodone is a strong opioid used increasingly as an alternative to morphine in the management of cancer-related pain. Studies to date have involved small numbers of people, and looked at stable cancer pain with low pain scores. It is therefore difficult to find real differences between drugs. Although some studies suggest some differences in adverse-effect profile, again, numbers are too small to draw definitive conclusions. Current available data suggest that oxycodone and morphine are similar in terms of efficacy, tolerability, and patient preference.

OPTION TRAMADOL New

Pain control
Compared with placebo Tramadol may be more effective at reducing pain intensity in people with moderate to severe cancer pain (low-quality evidence).

Compared with morphine We don't know whether tramadol is more effective at reducing cancer-related pain at 2–5 weeks (very low-quality evidence).

Compared with codeine We don't know whether tramadol is more effective at reducing cancer-related pain (very low-quality evidence).

Compared with dihydrocodeine We don't know whether tramadol is more effective at relieving prostate cancer-related pain (very low-quality evidence).

Need for rescue analgesia
Compared with placebo Tramadol may be more effective at 45 days at reducing the need for rescue analgesia in people with moderate to severe cancer pain (low-quality evidence).

Patient preference
Compared with morphine Tramadol may be the less preferred opioid when balancing between pain control and adverse effects (very low-quality evidence).

Compared with codeine We don't know whether people prefer tramadol to codeine (very low-quality evidence).

Compared with dihydrocodeine We don't know whether people prefer tramadol to dihydrocodeine for prostate cancer-related pain (very low-quality evidence).

Quality of life
Compared with placebo Tramadol may be more effective at reducing the proportion of people with serious limitations in Activities of Daily Living (a measure of quality of life) at 45 days (low-quality evidence).

Note
We found no clinically important results about tramadol compared with transdermal fentanyl, hydromorphone, methadone, or oxycodone in people with cancer-related pain.

For GRADE evaluation of interventions for opioids in people with cancer-related pain, see table, p 15 .

Benefits:

Tramadol versus placebo:
We found one RCT (36 people aged 18–60 years with moderate to severe cancer pain or cancer treatment-related neuropathic pain for at least 3 months, double blind parallel design) comparing tramadol (1–1.5 mg/kg every 6 hours) versus placebo. [26] It found that tramadol significantly reduced pain intensity over 45 days (measured on a 10-point scale where 0 = no pain: 2.9 with tramadol *v* 4.3 with placebo; P less than 0.001). It also found that tramadol significantly reduced the need for

rescue analgesia over 45 days compared with placebo (P less than 0.05, absolute numbers not reported). Tramadol significantly improved quality of life over 45 days compared with placebo as measured on the Activities of Daily Living (ADL) scale (proportion of people with serious limitations in ADL: 4/13 [31%] with tramadol *v* 10/12 [83%] with placebo; P = 0.008).

Tramadol versus morphine:
See benefits of morphine, p 2 .

Tramadol versus codeine:
We found one RCT (60 people with cancer pain, double-blind crossover design) comparing tramadol (40 mg every 6 hours) versus codeine (30 mg every 6 hours). The first study drug was given for 1 week, followed by the second study drug for 10 days (the first 3 days viewed as a washout period). [27] The dose of each drug was titrated as needed to achieve pain control to an average maximum of 68 mg every 6 hours of tramadol and 49 mg of codeine. Pain was assessed using a 10 cm visual analogue scale (VAS) (1–3 = mild pain, 4–6 = moderate pain, 7–10 = severe pain). An equivalence between codeine and tramadol of 1/1.3 was used. [27] At 1 week, before crossover, an analysis of 44/60 (73%) participants found no significant difference in pain between tramadol and codeine (mean VAS score: 4.1 with tramadol *v* 3.4 with codeine; reported as non-significant; P value not reported). Analysis of 37/60 (62%) participants after crossover found similar results (mean VAS score: 3.3 in each group; reported as non-significant; P value not reported). Analysis of patient preference in 34/60 (57%) participants found that half preferred tramadol and half codeine (significance not assessed).

Tramadol versus dihydrocodeine:
We found one controlled clinical trial (32 people with prostate cancer-related pain, double blind, crossover design, not reported if randomised but reported that baseline characteristics of all participants very similar) comparing slow-release tramadol 100 mg versus slow-release dihydrocodeine 90 mg twice daily for 14 days. [28] Dose was titrated to a maximum of tramadol 200 mg or dihydrocodeine 180 mg twice daily if pain score was 5 or greater on a 0–10 scale where 0 = no pain and 10 = unbearable pain. All participants also received haloperidol prophylactically to control nausea and vomiting. The trial did not directly compare tramadol versus dihydrocodeine when assessing pain relief, but assessed changes from baseline within each group. It found that both tramadol and dihydrocodeine reduced pain from baseline at 14 days (decrease in pain on scale from 0–10: 2.1 with tramadol, 2.4 with dihydrocodeine; P less than 0.05 for both groups *v* baseline). The controlled clinical trial found no significant difference in patient preference between tramadol and dihydrocodeine (proportion of people who expressed satisfaction: 91% with tramadol *v* 81% with dihydrocodeine; reported as non-significant for both outcomes, absolute numbers and P value not reported).

Tramadol versus transdermal fentanyl, hydromorphone, methadone, or oxycodone:
We found no systematic review or RCTs.

Harms:

Tramadol versus placebo:
The RCT found that tramadol significantly increased the proportion of people who had adverse effects compared with placebo (7/13 [54%] with tramadol *v* 0/12 [0%] with placebo; P = 0.003). [26] Adverse effects included nausea, somnolence, constipation, dry mouth, dizziness, and tiredness.

Tramadol versus morphine:
See harms of morphine, p 2 .

Tramadol versus codeine:
The RCT found no significant difference between tramadol and codeine in nausea, vomiting, constipation, or somnolence (nausea: 38% with tramadol *v* 47% with codeine group; vomiting: 31% with tramadol *v* 43% with codeine; constipation: 60% with either drug; somnolence: mean 1.3 hours with tramadol *v* 1.2 hours with codeine; reported as non-significant, P value and absolute numbers not reported for all outcomes).

Tramadol versus dihydrocodeine:
The RCT found no significant difference between tramadol and dihydrocodeine in nausea and vomiting (16% with tramadol *v* 28% with dihydrocodeine or sedation (28% in each group; reported as non-significant for both outcomes, P values not reported). However, it found that tramadol was associated with significantly less constipation than dihydrocodeine (25% with tramadol *v* 56% with dihydrocodeine; reported as significant, P value not reported).

Tramadol versus transdermal fentanyl, hydromorphone, methadone, or oxycodone:
We found no RCTs.

Comment: **Clinical guide:**
Tramadol has a weak mu-opioid effect compared with opioids such as morphine, and a weak monoaminergic effect compared with tricyclic analgesics. Unlike strong opioids, tramadol has a ceiling dose of 400 mg/24 hours. Because of the dose ceiling, it is not considered an alternative to morphine for severe cancer pain.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Morphine for cancer pain New option for which we identified 6 systematic reviews, [5] [6] [10] [12] [18] [19] and 12 RCTs comparing morphine versus other opioid analgesics. [7] [8] [9] [11] [13] [14] [15] [16] [17] [20] [21] [22] Morphine is the standard for the management of moderate to severe cancer pain and we found insufficient evidence to judge definitively how other opioids compare with it. Categorised as Trade-off between benefits and harms.

Codeine for cancer pain New option for which we identified one RCT that provided insufficient evidence to draw conclusions about codeine. [23] Categorised as Unknown effectiveness.

Dihydrocodeine for cancer pain New option for which we identified no RCTs. Categorised as Unknown effectiveness.

Fentanyl (transdermal) for cancer pain New option for which we identified four RCTs that provided insufficient evidence to assess effects of transdermal fentanyl. [24] [7] [8] [9] Categorised as Trade-off between benefits and harms.

Hydromorphone for cancer pain New option for which we identified two RCTs [11] [25] suggesting that hydromorphone may be as effective as morphine or oxycodone for pain relief and may cause fewer adverse effects than morphine. Categorised as Trade-off between benefits and harms.

Methadone for cancer pain New option for which we identified three RCTs [13] [14] [15] suggesting that methadone may be as effective as morphine for reducing pain and causes similar rates of adverse effects. Categorised as Trade-off between benefits and harms.

Oxycodone for cancer pain New option for which we identified one systematic review [18] and one RCT [20] suggesting that oxycodone and morphine may be equally effective at reducing pain and one RCT [25] suggesting that oxycodone and hydromorphone may also be equivalent. Categorised as Trade-off between benefits and harms.

Tramadol for cancer pain New option for which we found one RCT suggesting that tramadol reduced pain compared with placebo [26] and two RCTs [21] [22] suggesting that it may be as effective as morpine, although morphine seems to have a quicker onset of action. Categorised as Trade-off between benefits and harms.

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Disclaimer

TABLE **GRADE evaluation of interventions for opioids in people with cancer-related pain**

Important outcomes	Pain control, need for rescue analgesia, quality of life, patient preference, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of opioids in treating cancer-related pain?									
3 (273) [7] [8] [9]	Pain control	Morphine *v* fentanyl (transdermal)	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, open label RCT, and poor follow-up
2 (169) [7] [8]	Need for rescue analgesia	Morphine *v* fentanyl (transerdamal)	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, open label RCT, and poor follow-up
2 (267) [8] [9]	Patient preference	Morphine *v* fentanyl (transerdamal)	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, open label RCT, and poor follow-up
1 (100) [11]	Need for rescue analgesia	Morphine *v* hydromorphone	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, methodological weaknesses, and no washout between treatments. Directness points deducted for low pain scores, and uncertainty about applicability of results to clinical practice
3 (197) [13] [14] [15]	Pain control	Oral morphine *v* oral methadone	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and open label RCTs. Directness point deducted for comparing different disease severities
2 (55) [16] [17]	Pain control	Parenteral morphine *v* parenteral methadone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data, and incomplete reporting of results. Directness point deducted for inclusion of co-intervention
4 (198) [18] [20]	Pain control	Morphine *v* oxycodone	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
1 (20) [20]	Patient preference	Morphine *v* oxycodone	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
2 (60) [21] [22]	Pain control	Morphine *v* tramadol	4	–3	–1	–2	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and open label RCTs. Consistency point deducted for different results at different end points. Directness points deducted for inclusion of non-cancer pain and for uncertainty about equivalent doses
1 (20) [21]	Patient preference	Morphine *v* tramadol	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for no direct comparison between groups, and unclear outcome assessment
At least 3 RCTs (at least 342 people) [7] [8] [9]	Adverse effects	Morphine *v* fentanyl (transdermal)	4	–2	0	0	0	Low	Quality point deducted for incomplete reporting of results and open label RCT
1 (30) [23]	Pain control	Codeine *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
1 (30) [23]	Need for rescue analgesia	Codeine *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data

Important outcomes	Pain control, need for rescue analgesia, quality of life, patient preference, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (72) [24]	Pain control	Transdermal fentanyl *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and poor follow-up. Directness point deducted for recruiting participants with well-controlled pain
1 (72) [24]	Need for rescue analgesia	Transdermal fentanyl *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and poor follow-up. Directness point deducted for recruiting participants with well-controlled pain
1 (44) [25]	Pain control	Oxycodone *v* hydromorphone	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
1 (44) [25]	Patient preference	Oxycodone *v* hydromorphone	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results, and for sparse data
1 (36) [26]	Pain control	Tramadol *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
1 (36) [26]	Need for rescue analgesia	Tramadol *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
1 (25) [26]	Quality of life	Tramadol *v* placebo	4	–2	0	0	0	Low	Quality point deducted for sparse data and poor follow up
1 (60) [27]	Pain control	Tramadol *v* codeine	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and no intention-to-treat analysis
1 (60) [27]	Patient preference	Tramadol *v* codeine	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and no intention-to-treat analysis
1 (32) [28]	Pain control	Tramadol *v* dihydrocodeine	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, CCT and uncertainty about randomisation. Directness point deducted for no direct comparison
1 (32) [28]	Patient preference	Tramadol *v* dihydrocodeine	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and uncertainty about randomisation (CCT)

Type of evidence: 4 = RCT; 2 = Observational. CCT, controlled clinical trial; Consistency: similarity of results across studies. Directness: generaliseability of population or outcomes. Effect size: based on relative risk or odds ratio